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November 16, 1999

I would like to address the following comments to Jane Henney M.D., theCommissioner of the Food and Drug Administration, regarding FDA's implementation of Executive Order 13139. it is my understanding that this letter is being received within the time period open for comments, and that these comments will be published by FDA.

The impact of this Executive Order is to take final authority for use of investigational drugs and bioiogics by the US Department of Defense out of the hands of the FDA and place it in the hands of the President and Secretary of Defense, with FDA consultation.

Despite wide acknowledgment that the use of investigational medical products in Operations Desert Storm/Desert Shield and Operation Joint Endeavor did not comply with FDA requirements which accompanied FDA's waiver of informed consent , E. O. 13139 further weakens institutional oversight of the Department of Defense's use of these products.

1. Although it was required that an Institutional Review Board (IRB) be constituted to approve use of the investigational products, the Federal Register of October 5, 1999 on page 6 notes that an IRB constituted for this purpose at the time of Operation Desert Storm (ODS) recommended that informed consent be obtained. Another IRB reviewed similar material and did not make this suggestion The second IRB's comments were those used.

As has been seen in the example of potency testing to redate expired lots of anthrax vaccine, in which repeated tests are performed until the desired result is obtained, it appears that multiple IRBs can be constituted to advise on use of investigational new drug (IND) products in the same way, until one IRE3 produces the desired result. This flaunting of the meaning of the IRB requirement should not be allowed to stand.

2 President Clinton has added "the means for tracking use and adverse effects of the investigational drug" to the items that the Secretary of Defence shall submit to the FDA. Tracking of adverse effects is extremely important. However, the FDA rule 50.23(d)(I) (vii) refers to tracking only receipt of the product, and (xi) suggests only that "DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product." Thus no tracking of adverse events is mandated by FDA

What is required in order to evaluate ths safety profile of an IND product is medical followup of all recipients of an unlicensed product, prospectively, using active surveillance. Recipients of such products must be given the opportunity to report any and all adverse effects they experience following administration of the product. These data must then be regularly reviewed by civilian

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medical professionals so that a risk/benefit assessment for use of the product can be made In a timely manner. Limiting reporting of adverse effects to only those "expected" is far too narrow to obtain a safety profile for an experimental product which in most cases will be used on a large scale for the first time:

Without a requirement for this type of data gathering and analysis, it is unlikely to take place within a time frame that will protect servicemembers from use of products that are found, when the data are reviewed, to be more dangerous than originally anticipated.

3. The requirement that servicemembers be given written information about the IND product is excellent. However, oversight needs to be maintained in this area as welt. I have been informally told by servicemembers that they have received vaccines for malaria and Hepatitis C in the past year, without informed consent being obtained or written materials provided. Since there exist no licensed malaria or Hepatitis C vaccines in the US, servicemembers were given IND products, if their reports are correct, without adherence to FDA's IND guidelines.

To prevent the IND regulations from being ignored, I would suggest that a civilian committee be constituted to review all IND product use within the military. Such a committee would oversee the minutes of IRB deliberations, review the design of informed consent documents for accuracy and completeness, and review the signed consent documents provided by all those receiving IND products, to confirm full compliance with the regulations.

4. The Department of Defense and FDA have said that the intent of the original waiver 50 23(d). and by implication the current E.O. 13139, was only to use the ruling in very limited circumstances. It has been widely stated that the waiver was used for only two investigational products at the time of the Gulf War: pyridostigmine bromide and botulinum toxoid. However, unpublished minutes of DOD meetings and other materials in my possession suggest that a number of other investigational products were obtained for use in ODS and possiby given waivers by FDA: these include centoxin and a gamma globulin product unlicensed in the US.

The fact that other experimental products were to be used in ODS indicates that the use of the 23(d) waiver was not so restricted as Congress and the public have been led to believe. It negates the assertion that the drugs used were not "exotic," and it further indicates a coverup of use of experimental products which could have contributed to illness in Gulf War veterans. This concealment of the use of such products over the past nine years calls for serious outside oversight of any *and* all use of unlicensed medical products.

5 The use of old products is not addressed in E.O. 13139 or in the C.F.R. However, this is a critical area to explore. The DOD has noted that IND products are not labelled with an expiration date; therefore, technically they last forever. Even licensed products such as vaccines, when stored in bulk, are not assigned an expiration date, and they too "last forever." Documents making these assertions were included with my written testimony to the House Armed Services Committee Military Personnel Subcommittee of September 30, 1999. Products which would therefore be considered expired and unfit for use in the civilian sector are being used routinely on servicemembers The problem is compounded by the IND status of a product. in which no expiration date is assigned. The possibility that the DOD would maintain products in an IND rather than licensed status to take

advantage of this technicality exists. No requirement to characterize the composition of old vaccine or drug products and verify the absence of toxic degradants before use exists. FDA should address this issue, and consider the imposition of expiration dates on IND products and licensed products stored in bulk.

6. The amended regulations ask the **FDA** Commission& to review the waiver request for the President. This appears to be the only requirement for medical **oversight in** E.O. 13139. Is the FDA commissioner able to provide effective oversight? For IND products, there is likely to be no published information available, so the **FDA** Commissioner would be limited to **relying on** unpublished documents chosen for her review by DOD. Even in the case of anthrax vaccine, a licensed product, there are no published studies of human efficacy or safety. Therefore, no independently generated information is available for review by the FDA and other medical professionals. How can a thorough, critical review be carried out when it is likely that no data can be procured, except that provided for review by DOD?

7. Although E.O. 13139 does not address the potential use of IND products for civilians, the document "Department of Defense Comments on FDA Questions Regarding Interim Final Rule" included in the Congressional briefing packet does this. It states that , "[the interim rule]...should be broadened in two *ways.* First, it should be explicit that military operational *exigencies* other than combat are covered within the scope of the rule. Second, the issue of medical countermeasures against the threat of domestic terrorism involving chemical or biological weapons should be considered." This document ends with the statement, "The Office of Emergency Preparedness. DOD, and the FDA should work together to assure that medical personnel can use the best prophylactic and therapeutic products available against chemical and biological weapons in both the military and civilian contexts. This should be an urgent priority."

Thus it appears that the intent may be to eventually broaden use of IND products to civilians, in emergency situations, without informed consent. Congress and the FDA should be vigilant in preventing such an incursion into the rights of civilians to choose or refuse their own medical treatments

E.O. 13139 does broaden the use of IND products from wartime exigencies to "particular military operations " Congress and FDA should consider whether this definition sufficiently restricts use of such products to appropriate situations, and whether **it** opens the door to servicemembers being used as experimental subjects in the absence of military exigencies.

I appreciate the FDA's **consideration of these** issues as it reviews the implementation Of Executive Order 13139. Thank you.

Meryl Nass

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